Population Pharmacokinetic Study of Amoxicillin-treated Burn Patients Hospitalized at a Tertiary Swiss Centre

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Abstract

Objectives: To investigate the population pharmacokinetics (PK) of amoxicillin in ICU burn patients and the optimal dosage regimens.

Methods: Prospective study involving 21 consecutive burn patients receiving amoxicillin. PK data were analysed using non-linear mixed effects modelling. Monte-Carlo simulations assessed the influence of various amoxicillin dosage regimens with identified covariates on the probability to achieve a target (PTA) value of time during which free amoxicillin concentrations in plasma exceeded the minimal inhibitory concentration (*f*T>MIC).

Results: A two-compartment model best described the data. Creatinine clearance (CL_{CR}) and body weight (BW) influenced amoxicillin CL and central volume of distribution (V1), respectively. The median CL_{CR} (Cockcroft-Gault formula) was high (128 mL/min) with 25% of patients having CL_{CR} > 150 mL/min. The CL, V1 and $t_{½}$ values at steady-state for a patient with a CL_{CR} of 110 mL/min and BW of 70 kg were 13.6 L/h, 9.7 L and 0.8 h, respectively. Simulations showed that a target *f*T>MIC ≥ 50% was achieved (PTA > 90%) with standard amoxicillin dosage regimens (1-2 g q6-8 h) when the MIC was low (< 1 mg/L). However, increased dosages of up to 2 g/4 h were necessary in patients with augmented CL_R or higher MIC. Prolonging amoxicillin infusion from 30 min to 2 h had a favourable effect on target attainment.

Conclusion: This population analysis shows an increased amoxicillin CL and substantial CL PK variability in burn patients compared to literature data with non-burn patients. Situations of augmented CL_{CR} and/or high bacterial MIC target values may require dosage increases and longer infusion durations.

Keywords: Amoxicillin, pharmacokinetics, burn patients.

Introduction

Treating sepsis promptly and adequately in burn patients is crucial as it is still the predominant cause of morbidity and mortality despite major advances in hemodynamic and respiratory support (1-5). In this context, optimizing antibiotic dosage regimens to improve clinical outcomes and to avoid antibiotic resistance is desirable (6). However, this task is highly complex as it not only requires a well-trained multidisciplinary team but also extended knowledge of pharmacokinetic (PK) alterations due to burn trauma (7-9). Therapeutic drug monitoring (TDM) appears to be a useful intervention to ensure attainment of PK/pharmacodynamic (PD) surrogate indicators of antibiotic efficacy to counteract the well documented intervariability PK observed in this population (10-15). Moreover, TDM might also potentially improve burn patient outcomes (10, 12, 16, 17). Currently, the Bayesian forecasting approach for estimation of individual PK parameters represents the gold-standard approach for TDM (18, 19).

Amoxicillin is frequently used as a first-line antibiotic treatment in burn patients during the first weeks of hospitalization (14). It is partially metabolized by the hepatic system and lowly protein-bound (18%) (20). As this antibiotic is excreted in the urine (60% unchanged), its elimination is slowed in case of renal impairment. TDM of amoxicillin is available but rarely used in our institution, including in the Burn Centre, as beta-lactam antibiotics are often thought to have few dose-dependent side effects and a wide therapeutic margin (21).

Because significant PK changes of antibacterial agents have been reported in burn patients, such patients are considered as a special population in clinical PK studies (9, 22). For beta-lactams, most reports indicate increased values of drug CL and volume of distribution in burn patients compared to healthy subjects (9). Because of these alterations, dose requirements of antibiotics may be increased in this population. However, few reports have

addressed the PK profile in burn patients and are based on a small number of individuals. The use of a population approach to characterize amoxicillin PK and its variability and identify sources of variability has rarely been performed in burn patients.

In this context, our study aimed at determining the PK profile of intravenous amoxicillin given to adult patients with severe burns hospitalized in the Burn Centre of our hospital. The population model served to evaluate the PK/PD target attainment using standard and alternative dosage regimens of amoxicillin.

Materials and Methods

Ethics

This study was approved by the Institutional Review Board of the Centre Hospitalier Universitaire Vaudois and the Ethics Committee of the State of Vaud, Switzerland (protocole 195/13). Written informed consent was obtained from each patient.

Study design and setting

We prospectively and consecutively enrolled all burn patients admitted to the Burn Centre of our hospital who received a course of intravenous amoxicillin administered either alone or in combination with clavulanic acid from October 2013 to October 2016. The Burn Centre is a five-bed Swiss tertiary ICU nested in a 35-bed medical surgical ICU. This study was registered on the https://clinicaltrials.gov/ platform (Trial Registration: NCT01965340).

Data collection

Age, sex, weight, CL_{CR} (Cockcroft-Gault formula) and burn characteristics (including total burnt body surface area and Ryan score (23)) were collected from medical records for each

burn patient hospitalized during the study period. Data regarding amoxicillin administration (including date and time of administration, dose administered and duration of infusion) were prospectively collected from our computerized information system (Metavision; IMDsoft, Tel Aviv, Israel). For each episode of infection, the microorganism was systematically identified, if possible. The susceptibility of amoxicillin was determined using E-Test for each patient in whom the microorganism was identified (24, 25).

Antimicrobial treatment

Amoxicillin [Clamoxyl® (GlaxoSmithKline AG, Münchenbuchsee) or Co-Amoxi-Mepha® (Mepha Schweiz AG, Basel)] was dosed in accordance with the manufacturer's recommendations (1-2 g every 6–8 h in patients with normal renal function) and infused over 2 h (amoxicillin) or 1 h (amoxicillin/clavulanic acid) starting from the second dose (over 30 min for the first dose) according to our local guidelines. Indeed, amoxicillin/clavulanic acid solutions (diluted with 0.9% NaCl) have limited stability and, therefore, the maximal infusion time was set to 1 h. In contrast, as amoxicillin alone is more stable (stability of 3 h or 6 h when diluted in Ringer's lactate solution or 0.9% NaCl, respectively (20)), an extended perfusion (2 h) could be used. For patients with renal insufficiency, the dosage was adjusted according to the renal function estimated by the Cockcroft-Gault equation (eGFR < 30 ml/min: 500 mg–2 g q8-12 h; eGFR < 15 ml/min: 750 mg–2 g q24 h).

Blood concentration measurements

Blood samplings for the amoxicillin assay were performed at various time points. Trough levels were sampled on days 2, 4, 6 and 8. Additional samples were obtained every 2 days in a few patients who received a course longer than 8 days. Random levels were sampled on day 6 and day 8. A rich amoxicillin kinetic profile was obtained on one occasion for most patients

(18 out of 21, including one patient with two rich profiles) at the following sampling times: 0, 1, 2, 3, 4 and 5 h after the end of the infusion. The exact times were adjusted according to the infusion duration.

Determination of amoxicillin concentrations

Amoxicillin plasma levels were determined using a multiplex assay by ultra-performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS) requiring 100 µL of plasma for the simultaneous quantification within 9 min of 12 most recommended and frequently used antibacterial drugs (see **Supplemental Material**)(26). As no assay method was available for clavulanic acid, its concentration was not determined in this study. Blood samples were directly sent to the laboratory after sampling and were stored at -80°C until the analysis. Analyses were performed within 6 hours during the week. Samples collected over the weekend were analyzed the following Monday afternoon.

Population PK model building

NONMEM version 7.1.0 (ICON Development Solutions, Ellicott City, MD, USA) was used to analyse amoxicillin plasma concentrations versus time data using a non-linear mixed-effects modelling approach. The first-order conditional estimation with the interaction algorithm was selected for all runs. We assumed log-normal distributions of PK parameters, i.e. an exponential model for interindividual variability. First, the best structural model and residual error models were identified. One-, two- and three-compartment open linear models were evaluated. For the residual error, proportional, additive and combined (additive plus proportional) error models were tested.

Next, covariate model building was performed using the Stepwise Covariate Model building tool of Perl Speaks to NONMEM (27). This tool permits forward selection and

backward deletion of covariates in a model in a comprehensive manner. The following covariates were investigated: sex, total body surface area, serum albumin, serum creatinine, CL_{CR} (estimated by the Cockcroft-Gault equation), actual body weight (BW), BW on admission (BW_{ADM}), BW gain (defined as BW – BW_{ADM} when BW > BW_{ADM} and zero otherwise), and BW loss (defined as BW_{ADM} – BW when BW_{ADM} > BW and zero otherwise). Linear relationships were tested for categorical covariates, while linear and power functions were tested for continuous covariates. The change in the objective function value (OFV) was used to assess the influence of covariates, assuming a chi-squared distribution of the OFV, with one degree of freedom for each addition of a linear power relation. Statistical significance was set at a p-value of 0.05 for forward selection and 0.01 for backward deletion.

Final model evaluation

Internal model validation was based on standard criteria (28): the OFV as described above, parameter estimates along with their standard errors, plots of observed amoxicillin concentration versus population and individual predictions, and plots of conditional weighted residuals (29). A bootstrap analysis (n = 1000 samples with replacement from the original dataset) was carried out with the PsN tool kit to check the uncertainty of parameter estimates and derive the 95% CI. A visual predictive inspection was also performed by comparing the observed amoxicillin concentration with model-based simulations (n = 1000 samples for each patient)(30).

Dosing simulations

PK/PD simulations were performed based on the final model to investigate the influence of amoxicillin dose, dose interval, infusion duration and covariates (renal function) on the probability to achieve a target exposure for amoxicillin. All simulations and calculations of

probabilities of target attainment were done with the Pmetrics R package (31). Mean and variance of parameters of the final model estimated with NONMEM were imported into Pmetrics. We tested three amoxicillin doses (0.5, 1 and 2 g), five dosing intervals (4, 6, 8, 12 and 24 h), and two infusion times (30 min and 2 h). As CL_{CR} was found to influence amoxicillin CL, we considered six levels of renal function: 15, 30, 60, 100, 150 and 200 mL/min. For each condition, 500 virtual patients were created based on parameter estimates and covariates retained in the final NONMEM model. Amoxicillin CL values were randomly sampled based on the final estimates of mean and variance. The Q and V2 values were fixed to their final NONMEM estimates for all subjects. Since BW influenced V1, this value changed as a function of BW. BW was sampled from a log-normal distribution in the form of $89 \times \exp(\eta_{BW})$, with $\eta_{BW} \sim N(0, 0.184^2)$. These values were representative of the average BW (89 kg) during antibiotic therapy and variability in a group of 39 burn patients from our Burn Centre who received a beta-lactam antibacterial agent (data not shown), including the 21 burn patients involved in this study.

Steady-state (i.e. after 10 days of therapy) amoxicillin concentration profiles were simulated for each condition. Then, we derived probabilities of target attainment (PTA) using the dedicated function in Pmetrics. The PK/PD target was defined as a percentage of time during which the free amoxicillin concentration in plasma exceeds the MIC (*f*T>MIC). Two targets were considered: a target of *f*T>MIC ≥ 50% usually recognized as efficient for β-lactams (such as penicillins and carbapenems) (32-35), and a more conservative target of *f*T>MIC = 100%, which seems to be associated with better outcomes in critically ill patients (11, 36). We considered MIC values of 0.25, 0.5, 1, 2, 4, 8 and 16 mg/L as 8 mg/L is the highest amoxicillin MIC breakpoint value for several Gram-negative organisms, including *Escherichia coli*, according to the European Committee on Antimicrobial Susceptibility Testing (37). We assumed a free fraction of 82% for amoxicillin (38). In addition, we

considered 90% as an optimal PTA to be achieved, as suggested by the European Medicines Agency (39).

The influence of BW on PTA was also examined using the same approach. We considered situations of low weight (50 kg), standard weight (70 kg), overweight (100 kg) and obesity (150 kg) as well as three levels of renal function (30, 100 and 200 mL/min) for each weight. A dosage regimen of 1 g q8h (infused over 30 min) was simulated in 500 virtual patients in all 12 conditions, and steady-state concentrations were analysed.

Results

Patient characteristics and microbiological data

A total of 185 amoxicillin concentrations were obtained from 21 burn patients aged from 16 to 93 years. The patients' body weight on admission ranged from 60 to 132 kg. **Table 1** presents the characteristics of the population. There was a large majority of male patients. The median CL_{CR} was high (128 mL/min), with 25% of patients having CL_{CR} > 150 mL/min. The median BW on admission was 72.4 kg, with a coefficient of variation of 22%. Limited intra-individual variability was observed in BW during the course of amoxicillin (± clavulanic acid) therapy, with a median change in BW of -2.3% (minimum, -11.4%; maximum, +10.6%). Of note, some patients had several episodes of infection that were treated by amoxicillin (± clavulanic acid). Microorganism identification with susceptibility was obtained at least once for 16 out of 21 patients. Two different bacteria were identified in the same sample for three patients, and one patient presented the same bacteria (*Staphylococcus aureus*) in two distinct tissue samples. As a result, a total of 20 susceptibilities were determined. **Table 2** summarizes the microbiological data.

Population PK model

The final model was a two-compartment model with the following parameters: amoxicillin CL, central (V1) and peripheral (V2) volumes of distribution, and intercompartmental clearance (Q).

Residual variability was best described by a combined additive and proportional residual error model. The stepwise covariate modelling approach identified CL_{CR} and BW as covariates influencing amoxicillin CL and V1, respectively. CL_{CR} was found to influence amoxicillin CL in a linear manner, and V1 was allometrically scaled to the actual BW. Amoxicillin CL was the only random PK parameter, while the others had a fixed, estimated value. Models incorporating between subject variability on V1, V2 and Q were tested. As they either did not improve the model fit or poorly estimated the corresponding random effects (high standard errors), interindividual variabilities were not estimated for those parameters in the final model. Interoccasion variability could not be tested owing to the sampling design, which prevented from discriminating between interoccasion and intrapatient variabilities. **Table 3** displays the final estimates of population PK parameters, bootstrap estimates as well as parameter–covariate relationships. All parameters were estimated with acceptable precision.

Figure 1 shows the plots of conditional weighted residuals versus population predictions and time. Most residuals were within the expected range (-2; +2), and no major trend was observed versus prediction or time. The prediction-corrected visual predictive check obtained with the final model is shown in **Figure 2**. As a good agreement was observed between measured amoxicillin concentrations and model-based predictions (**Figure 3**), the model was deemed to be appropriate for further dosing simulations.

Dosage regimen simulations

The Monte-Carlo simulation results are summarized in **Figure 4**. As expected, when all other factors were kept constant, the values of *f*T>MIC and PTA decreased with increasing renal function and MIC values.

Considering *f*T>MIC ≥ 50% as the target, in patients with normal renal function (CL_{CR} = 100 mL/min), the standard dosage regimens with a 30-min infusion of 1-2 g q6-8 h were adequate for MIC values ≤ 2 mg/L but failed to achieve 90% PTA for higher MIC values. For a MIC of 8 mg/L, such a PTA was only achieved with the most intensive dosage of 2 g/4 h and extended infusion (2 h) of 1 g/4 h or 2 g/6 h. The results were quite similar in patients with moderately impaired renal function (CL_{CR} = 60 ml/min), with 2 g/8 h administered as a 2-h infusion also being effective for high MIC values. In order to achieve the target of *f*T>MIC = 100%, regimens of 1 to 2 g administered every 4 h were necessary for MIC values ≤ 2 mg/L. However, for a high MIC of 8 mg/L, even an extended infusion of 2 g q4 h failed to achieve 90% PTA in simulated patients with CL_{CR} = 100 ml/min.

In patients with augmented renal clearance (200 mL/min), the minimum dose to achieve the desired 90% PTA for the low target (*f*T>MIC ≥ 50%) with MIC values ≤ 1 mg/L was 1g q6 h (**Figure 4**). For higher MIC values, prolonging the infusion duration was effective for obtaining a higher PTA, and a 2-h infusion of 2 g every 4 h was the only regimen associated with PTA > 90% for a MIC of 8 mg/L. None of the tested regimens was associated with acceptable PTA for the high target when the MIC was > 2 mg/L.

In patients with renal impairment (15 and 30 mL/min), reduced dosages (0.5 or 1 g q12h) appeared to be adequate for low MIC values but were not sufficient for MIC values as high as 8 mg/L. In this case, a standard dosage (1-2 g q6-8 h) appeared necessary to achieve

286 *f*T>MIC ≥ 50%, while regimens of 1 g q4 h and 2 g q4 h were necessary to achieve *f*T>MIC =
287 100% with acceptable PTA in patients with CL_{CR} of 15 and 30 ml/min, respectively.

288 BW had a limited influence on *f*T>MIC and PTA, as shown in **Table 4**. The index
289 *f*T>MIC slightly increased with an increasing BW as a result of a decrease in the distribution
290 (K12 = Q/V) and elimination rate constants (Ke = CL/V). However, even a three-fold increase
291 in BW only had a modest effect on PTA.
292

293 ## Discussion

294 Although amoxicillin is frequently prescribed in patients with severe burns, to the best
295 of our knowledge, this is the first population analysis carried out in this population. Literature
296 regarding the PK of amoxicillin in non-burn patients exists but is scarce (36, 40-42). Our
297 study provides several insights regarding the PK and dosage requirements of amoxicillin in
298 this population with known distinct PK characteristics. The PK of burn patients is indeed
299 altered due to different phenomena, such as capillary leak syndrome, mechanical ventilation,
300 hypoalbuminemia, extracorporeal circuits and post-chirurgical drains; in addition, significant
301 burn injuries themselves might increase the volume of distribution of hydrophilic drugs (43-
302 48).

303 Our results are in good agreement with a recent population PK study of
304 amoxicillin/clavulanic acid in 13 ICU adult patients (36), with comparable patient
305 characteristics (except for burns). While the typical values of volumes of distribution were
306 similar (V1 and V2), patients in the present study showed a 21% increased CL and a 22%
307 increased Q in patients with normal renal function (CL_{CR} of 110 mL/min) compared to the
308 ICU patients without burns. Our results confirm the increase in CL reported for other beta-
309 lactam agents in burn patients, irrespective of renal function (10, 15). We did not observe any
310 difference in amoxicillin volume of distribution in comparison to the non-burn population

(36, 49, 50). The covariate analysis confirmed that CL_{CR} influences amoxicillin CL, as previously described (36). We also found that BW influences V1, suggesting an approximate doubling of this value from 70 kg to 132 kg. This will reflect in a slightly longer elimination half-life in overweight patients. Renal function explained 35% of the initial estimated interpatient variability on amoxicillin clearance, which remains still largely unexplained. This large variability could be the due to several factors related to patients' characteristics, burn consequences and medical support that can affect drug concentrations.

In critically ill patients (including burn patients), evidence suggests that patients may have a higher CL_{CR} even in the presence of normal plasma creatinine concentrations (51, 52). An augmented CL_R (i.e. CL_{CR} > 130 mL/min) has been reported to occur in 15–65% of ICU patients including burn patients and therefore increasing the risk of subtherapeutic concentrations in this population (15, 53). Based on our simulations, our data showed that in patients with a CL_{CR} = 150 to 200 mL/min, the standard dosage achieved the desired 90% PTA only for cock values < 1 mg/L. In those patients, dosages as high as 2 g or 4 g appear necessary to achieve $fT>MIC \geq 50\%$ for the highest MIC breakpoint (8 mg/L). Prolonging the amoxicillin infusion from 30 min to 2 h was also a way to increase the target attainment. As more aggressive pathogens are commonly found in the ICU, the prescription of antibiotics has to be adapted and carefully monitored among burn patients (10). The standard amoxicillin dose of 1-2 g q6-8 h results in adequate exposure ($fT>MIC \geq 50\%$) for both low and normal CL_{CR} in the case of MIC values of ≤ 2 mg/L. However, a higher dosage regimen should be used to treat burn patients infected by microorganisms with higher MIC. This may be especially relevant for the treatment of infection caused by Enterobacteriaceae with amoxicillin/clavulanic acid, as those bacteria often display high MIC values ranging from 2 to 8 mg/L.

335 Achieving *f*T>MIC = 100% with acceptable PTA for MIC values as high as 8 mg/L
336 was only possible in patients with severe renal impairment. In burn patients with normal or
337 augmented renal clearance, our results showed that achieving this target was hardly possible
338 even with the highest dosage of amoxicillin (12 g/day) and repeated extended infusions. Yet,
339 the clinical benefits of targeting *f*T>MIC = 100% remains unclear. In the DALI study
340 performed in critically ill patients who received intravenous beta-lactams, there was no
341 difference in the predictive value of positive clinical outcomes following either *f*T>MIC =
342 100% or *f*T>MIC ≥ 50% (11). In addition, targeting *f*T>MIC = 100% in all burn patients
343 would require larger doses and concentrations of amoxicillin that could increase its toxicity
344 without a thorough monitoring by TDM. Indeed, adverse reactions such as crystalluria have
345 been reported with the use of high doses of amoxicillin (54, 55). Unlike renal function, inter-
346 individual changes in BW did not appear to have a clinically relevant influence on amoxicillin
347 PD in adult burn patients.

348 Our simulation results are somewhat different from those described by *Carlier et al*
349 (36). They reported that a *f*T>MIC of 50% or even 100% would be achieved in most ICU
350 patients treated with standard doses of amoxicillin (3–4 g in three or four administrations per
351 day), except for the conditions of augmented CL_R combined with the highest bacterial MIC.
352 Our less optimistic results in burn patients are likely due to the increased Q and CL values
353 discussed above. In addition, the proportion of simulated patients associated with successful
354 treatment was not clearly stated in the work by *Carlier et al.*

355 As shown for other time-dependent beta-lactam agents (56, 57), increasing the
356 infusion time of amoxicillin may be a simple way to optimize *f*T>MIC and drug response.
357 Amoxicillin combined with clavulanic acid is less stable than amoxicillin alone due to the
358 degradation of clavulanic acid catalysed by both acids and bases when dissolved in aqueous
359 solution (58). However, a recent study has demonstrated that amoxicillin alone is stable

360 enough to be administered as a continuous infusion and that the combination of amoxicillin
361 and clavulanic acid is stable for 2 h (58). As our data showed that prolonging the infusion
362 duration was effective for obtaining a higher PTA in burn patients treated with amoxicillin,
363 we therefore recommend that an extended infusion of 2 h could be used in cases of infections
364 caused by microorganisms with high MIC values.

365 Optimizing antibiotic exposure in the burn population is of high importance as 60% of
366 these patients fail to reach the PK/PD target of *f*T>MIC = 100% while receiving betalactams
367 (12). In order to counteract the PK variability observed in this frail population, it has now
368 been demonstrated that TDM is a valuable intervention that should be widely used in order to
369 reach and maintain the antibiotic therapeutic target (10, 12, 14, 15).

370 Our study had a prospective design and included all burn patients admitted consecutively to a
371 tertiary hospital. Nevertheless, this study has several limitations. First, as burn patients
372 constitute a specific and difficult population to study, the sample size is limited compared
373 with population PK standards. However, quite rich amoxicillin concentration data were
374 available, and PK parameters were precisely estimated. Second, as our laboratory could not
375 dose clavulanic acid, only the amoxicillin concentration could be analysed and studied for this
376 work. Further research is necessary to investigate the potential PK changes of clavulanic acid
377 in burn patients and to define the PK/PD in this population. However, amoxicillin is
378 considered as the main therapeutic agent as clavulanic acid has a very weak antibacterial
379 activity and literature suggests that clavulanic acid has no influence on amoxicillin PK and
380 vice-versa (59). Third, even though research is active on the field, it is still unclear which
381 PK/PD target should be aimed for in critically ill patients (including the burn population)(11,
382 12, 14) and experimental studies have shown that the values of fT>MIC required to produce a
383 given effect may vary between beta-lactams (35). Fourth, this work focused only on efficacy
384 targets and no upper threshold for toxicity endpoints was evaluated. Owing to the large

385 therapeutic window of amoxicillin, this should not present an important limitation to our
386 results. Finally, simulations performed outside the data range of data should be handle
387 cautiously. Nevertheless, this may be an adequate approach when the covariate-parameter
388 relationships have a rational basis. Regarding body weight, the use of allometric scaling to
389 describe the relationship between V1 and BW is a reasonable approach for simulating the
390 effect of weight on the PK based on the theories of allometry and scaling (60). Regarding
391 renal function, the simulation was based on the linear correlation found between amoxicillin
392 clearance and creatinine clearance which is in accordance with renal clearance concepts.

393 In conclusion, to the best of our knowledge, this is the first population analysis of
394 amoxicillin PK data in burn patients showing increased typical values and important
395 variability in amoxicillin CL compared to literature data with non-burn patients. This work
396 highlights the need for a higher dosage and a longer infusion of amoxicillin in burn ICU
397 patients with augmented CL_R infected by microorganisms with high MIC values.

List of Abbreviations

BW	Body weight
BW_{ADM}	Body weight on admission
CL	(Body) clearance
CL_{CR}	Creatinine clearance
ECOFFs	Epidemiological cut-off values
HPLC-MS/MS	High-performance liquid chromatography coupled with tandem mass spectrometry
ICU	Intensive care unit
MIC	Minimum inhibitory concentration
OFV	Objective function value
PK	Pharmacokinetic
PD	Pharmacodynamic
Q	Intercompartmental clearance
TDM	Therapeutic drug monitoring
V1	Central volume of distribution
V2	Peripheral volume of distribution

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Author contributions

CC, YQ, EP, PV and AF designed the study. AF and OP collected the data. CC, AF and SG analysed the data. AF, SG, CC, YQ, PE, OP and FS wrote the manuscript. All authors contributed to and approved the final version of the manuscript.

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Figure Legends

Figure 1. Model-derived conditional weighted residuals versus population predictions (upper panel) and time (lower panel).

Figure 2. Prediction-corrected visual predictive check obtained with the final model. The open circles represent the observed concentrations. The grey solid and dashed lines represent the median and the 5^{th}/95^{th} percentiles of the observed concentrations, respectively. The dark and light grey areas represent the 95% CI of the simulated median and 5^{th}/95^{th} percentiles, respectively. Of note, three observations greater than 100 mg/L are not shown for ease of graphical display (105.7, 134.4 and 198 mg/L).

Figure 3. Observed vs. population/individual predictions (linear scale). Circles represent population predictions and black dots individual predictions. The line is y = x.

Figure 4. Probability of target attainment as a function of the MIC and dosage regimen for six stages of renal function. IT indicates infusion time. The left and right panel shows the results for the low (*f*T>MIC ≥ 50%) and high (*f*T>MIC = 100%) pharmacodynamic target respectively.

634 **Table 1. Characteristics of the burn patients who received amoxicillin**
635

Characteristic		Value
Number of patients		21
Male, *n* (%)		16 (76.2)
Age (years), mean (± SD)		50.1 (24.3)
Body weight at admission (kg), median (IQR)		72.4 [67.0–83.6]
Initial CL_{CR} (mL/min), median (IQR)*		128 [65–150]
TBSA affected (%), median (IQR)		23 [12.5–44]
	< 20 (n, %)	7 (33.3)
	20–40 (n, %)	9 (42.9)
	41–60 (n, %)	2 (9.5)
	> 60 (n, %)	3 (14.3)
SAPS II, mean (± SD)		35.9 (18.6)
Ryan score, median (IQR)		1 [1–2]
Inhalation lesions, *n* (%)		16 (76.2)
Length of ICU stay, median (IQR)		23 [13.0–39.5]
Mortality in the burn ICU, *n* (%)		2 (9.5)

636
637 ***** Using Cockcroft and Gault formula.
638
639 **IQR:** Interquartile range; **SAPS II**: Simplified Acute Physiology Score; **SD**: Standard deviation;
640 **TBSA**: total body surface area.

641 **Table 2. Microbiological data**
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	Number of isolates	Median MIC (min–max)	Antimicrobial therapy
Gram-negative bacteria	5	2 (1–4) mg/L	Amoxicillin + clavulanic acid (n = 5)
Gram-positive bacteria	15	0.5 (0.016–2) mg/L	Amoxicillin (n = 3) Amoxicillin + clavulanic acid (n = 12)

644 Gram-negative species: *Haemophilus influenzae* (n = 2), *Klebsiella pneumoniae*, *Citrobacter koseri*, *Pantoea*
645 *spp.*
646 Gram-positive species: *Staphylococcus aureus* (n = 6), *Streptococcus pneumoniae* (n = 5), *Streptococcus bovis*,
647 *Enterococcus faecalis*, *Granulicatella adiacens*, *Bacillus spp*.

Table 3. Population PK parameters of amoxicillin

Parameter	Structural model mean estimate (RSE)	Covariate model mean estimate (RSE)	Bootstrap mean estimate (95% CI)
Fixed effects			
CL (L/h)	13.1 (12%)	13.6 (8%)	13.7 (11.5–16.5)
θ_{CLCR_CL}	-	0.57 (25%)	0.53 (0.19–0.79)
V1 (L)	10.1 (25%)	9.73 (20%)	9.6 (4.5–16.4)
Q (L/h)	20.8 (31%)	20.1 (24%)	20.2 (12.6–52.5)
V2 (L)	16.6 (15%)	17.6 (14%)	17.4 (13.0–24.2)
Random effect			
ωCL (CV%)	57.3 (16%)	37.3 (19%)	36.0 (21.7–53.2)
Residual variability			
Proportional error (%)	34.4 (20%)	37 (19%)	34.6 (22.1–47.5)
Additive error (mg/L)	0.59 (31%)	0.08 (10%)	0.08 (0.07–0.93)

CL: clearance, **V1**: central volume of distribution, **RSE**: relative standard error; **95% CI**: 95% confidence interval, $\boldsymbol{\theta_{CLCR\_CL}}$ proportional increase in CL elimination as a function of CL_{cr}, **ωCL**: interpatient variability on CL.

The final models are as follows:

$TV_{CL} = CL*(1 + \theta_{CLCR\_CL}*(CL_{CR} – 110))$

$TV_{V1} = V1 *(BW/70)$

where CL_{CR} is estimated by the Cockcroft-Gault equation (mL/min), 110 ml/min is average CLCr in our populationand BW is body weight (kg).

659 **Table 4. Probability of target attainment stratified by body weight and renal function**
660 **for a dosage of 1 g q8 h and a MIC of 8 mg/L**
661

CL_{CR}	Body weight	*f*T>MIC	PTA *f*T>MIC ≥ 50%	PTA *f*T>MIC = 100%
30 mL/min	50 kg	0.65 (0.24)	0.69	0.17
	70 kg	0.68 (0.24)	0.73	0.21
	100 kg	0.72 (0.24)	0.77	0.26
	150 kg	0.76 (0.23)	0.82	0.32
100 mL/min	50 kg	0.34 (0.18)	0.16	0.008
	70 kg	0.36 (0.19)	0.19	0.01
	100 kg	0.38 (0.20)	0.22	0.02
	150 kg	0.42 (0.21)	0.27	0.04
200 mL/min	50 kg	0.18 (0.10)	0.012	0
	70 kg	0.19 (0.10)	0.018	0
	100 kg	0.21 (0.11)	0.03	0
	150 kg	0.23 (0.12)	0.04	0

662

663 **CL_{CR}**: Creatinine clearance, ***f*T>MIC**: Cumulative percentage of a 24 h period that the
664 unbound fraction of a drug exceeds the MIC at steady-state pharmacokinetic conditions,
665 **PTA**: probability of target achievement.

666 **Figure 1**

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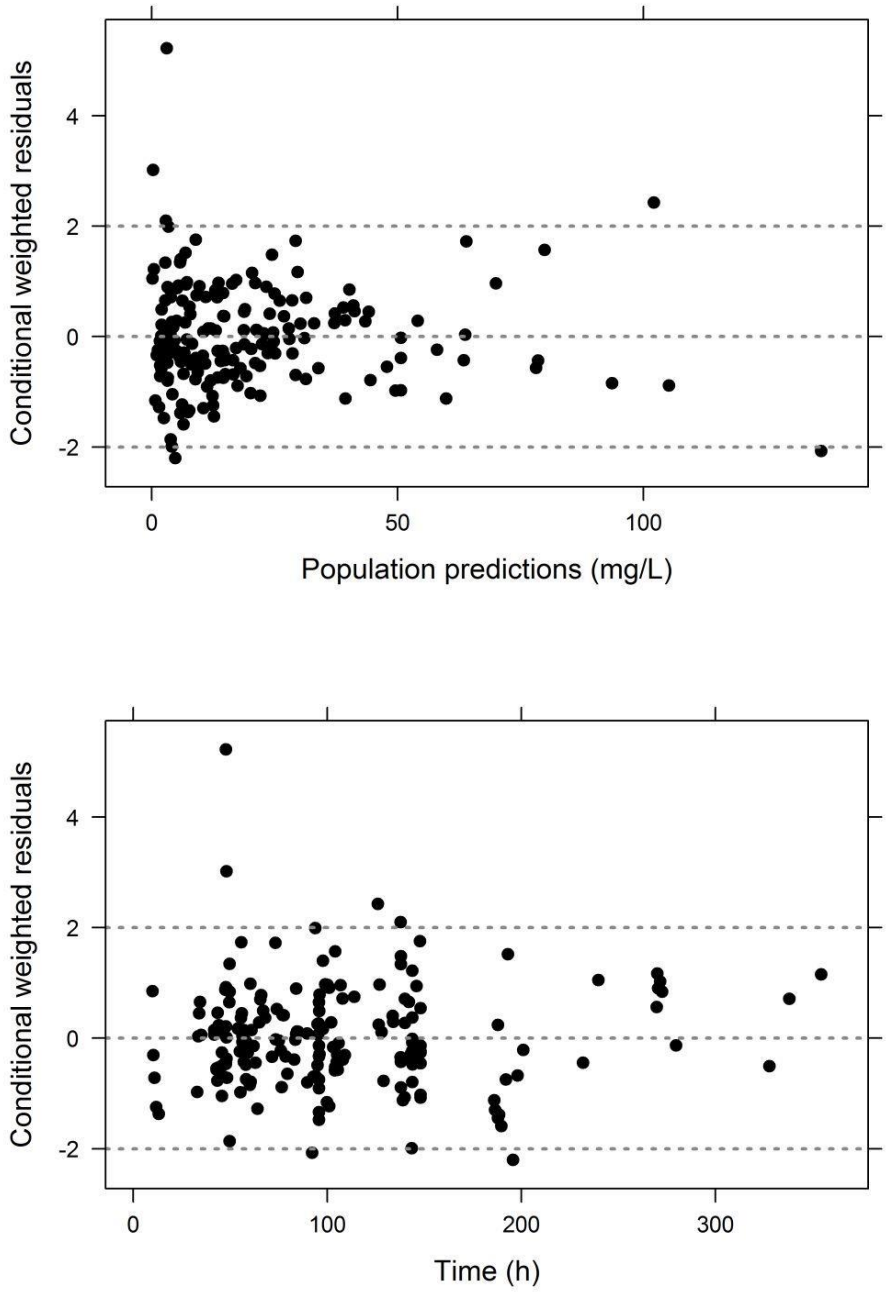

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670 **Figure 1.** Model-derived conditional weighted residuals versus population predictions (upper

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672 **Figure 2**

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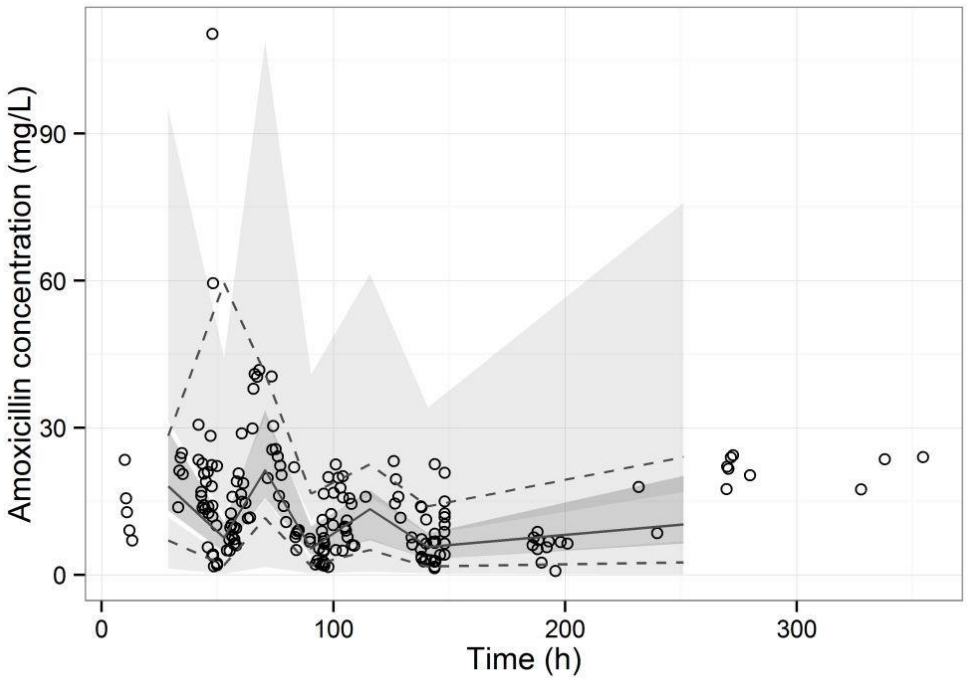

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682 **Figure 3**

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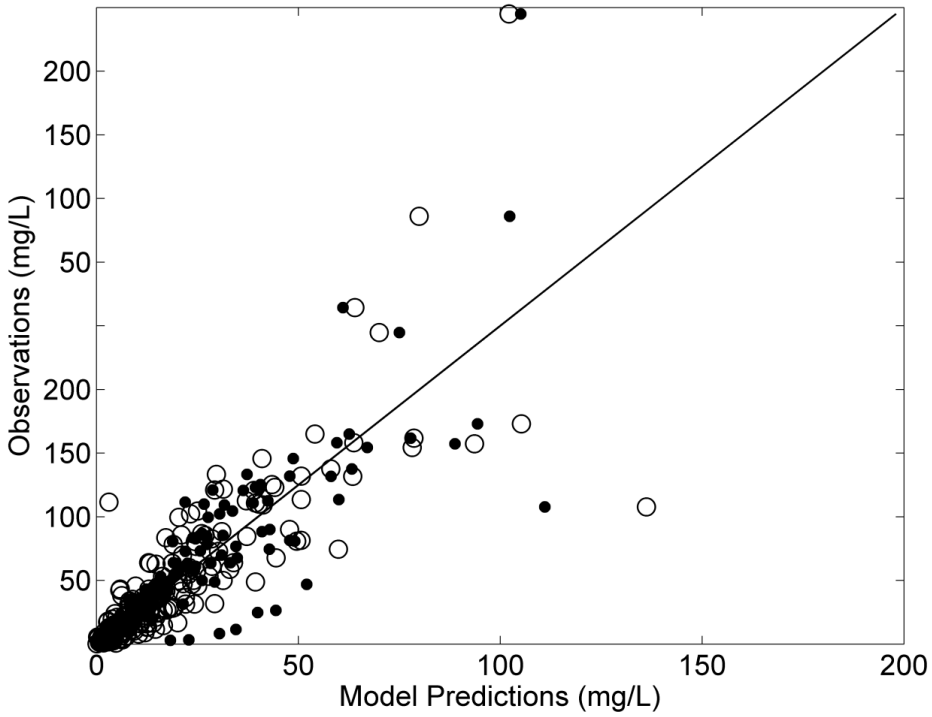

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698 **Figure 4**

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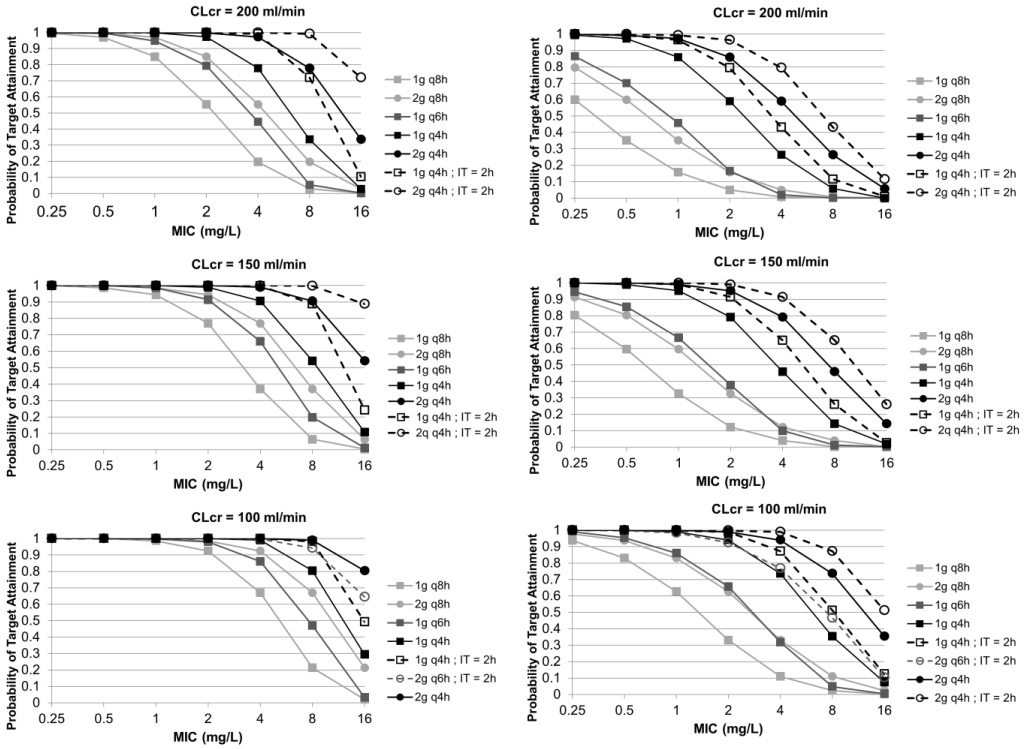

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713 **Figure 4 (continued)**

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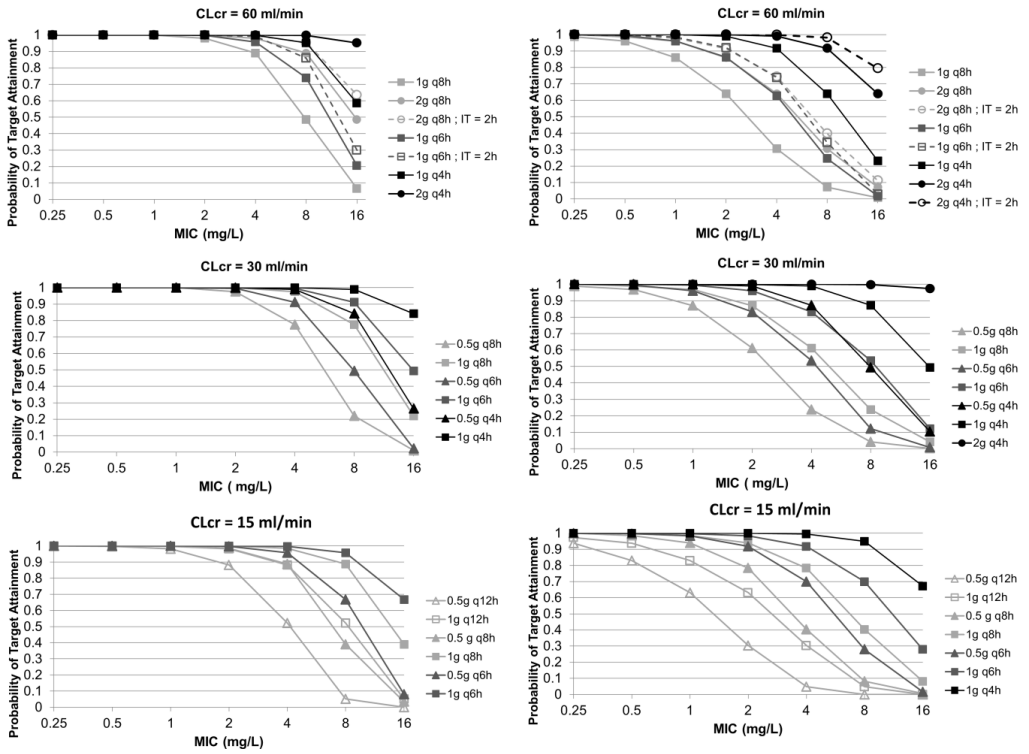

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